REMARKS

Upon careful review of the remarks presented in this reply, the Examiner should agree that the claimed invention is patentable and that this application is in good condition for allowance.

Regarding the Claim Amendments:

The amendments to the claims add no new matter. Claims 7, 12, 23, 24, and 25 have been canceled. Claim 1 has been amended to include the limitations of claims 7 and 12. Claim 26 has been rewritten in independent form.

Claims 6, 8, 11, 16, and 20 have been amended to make it clear that the recited weight percentages are "by weight of the total weight of the rate-controlled release particles." Support for these amendments can be found on page 12, indicated lines 24 – 26 of the Specification, which is reproduced below, for the Examiner's convenience:

> The polymeric matrix component is used in amounts of from 40 to 70, preferably of from 50 to 65% b.w. of the total weight of the particles.

The amendment to claim 8 also changes the dependency from claim 7, which has been canceled, to claim 1.

Regarding the Objection to the Amendment to the Specification:

The amendment to the Specification filed on September 1, 2006, adds no new matter. First, the Examiner has acknowledged that the error that was corrected was an *obvious error*, because the Examiner stated that "[t]he original data presented at page 15 is obviously not right...."[1] The Examiner is again reminded of the appropriate legal standard for determining whether an amendment to correct an obvious error constitutes new matter.

[1] Page 2, lines 9 – 10 of the final Office action mailed March 13, 2007.

"An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction."[2] As acknowledged by the Examiner a skilled artisan would recognize the existence of the obvious error. However, the Examiner has not considered whether a skilled artisan would have recognized the appropriate correction. Instead, the Examiner speculates as to what other corrections might "make sense,"[3] suggesting that changing "1, 2, 3, 4, 5, [6,] 7 and 8 in the table to 100, 200, 300, 400, 500, 600, 700, and 800"[4] could also "make sense." Thus, the Examiner has clearly objected to the amendment on an inappropriate standard. Again, the appropriate legal standard is not whether another change might make sense, but whether a skilled artisan would have recognized the appropriate correction. Under this standard, the objection cannot properly be maintained. A skilled artisan would surely have enough skill to determine that a typographical error in the table header occured, whereby the unit of time for the sixth column was listed as minutes rather than hours. Since a skilled artisan would have immediately recognized the appropriate correction to this obvious error, the amendment did not introduce new matter. The objection should be withdrawn.

Regarding the Outstanding Rejection:

In the final Office action of March 13, 2007, the Examiner rejected claims 1, 2, 4, 6 – 8, 10 – 16, and 20 – 25 under 35 U.S.C. §103(a) over *Andries et al.* (US 6,197,779), in view of *Goertz et al.* (US 4,801,460), *Nakamichi et al.* (US 5,456,923), *Sasatani et al.* (US 5,876,760) and *Takada* (US 5,350,741) and in further view of *Baert* (EP 0 872 233).

"Under §103, the scope and content of the cited art are to be determined; differences between the cited art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved."[5] The present rejection is based on a combination of references, however, the Examiner will certainly agree that in order to

[2] In re Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971).
[3] Page 2, line 11 of the final Office action mailed March 13, 2007.
[4] Page 2, lines 11 – 12 of the final Office action mailed March 13, 2007.
[5] Graham v. John Deere, 383 U.S. 1, at 17 – 18, 148 USPQ 459 (1966).

properly ascertain the differences between the cited art and the claims at issue, each reference must first be considered in turn, as a whole, including portions that teach away from the present invention.

Independent claim 1, as amended, relates to rate-controlled release particles, which comprise:

- a compound of the formula I to VI as an active ingredient,
- a polymer matrix , and
- from 5 to 25 % by weight of hydroxypropyl methyl cellulose (HPMC).

Claim 1, as amended also imposes the following limitations:

- The polymer matrix of claim 1, must consist of a homo- or copolymer of N-vinylpyrrolidone, in an amount from 40 to 70 % by weight of the total weight of the particles.
- The rate-controlled release particles must comprise the active ingredient as a solid dispersion in the polymer matrix.
- The rate-controlled release particles must be obtained by forming a homogeneous mixture of the components in the form of a melt, extruding the mixture, and shaping the extrudate.

Claims 2, 4, 6, 8, 10, 11, 13 – 16, and 20 – 22 depend from claim 1. Of course, "[i]f an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious."[6]

The *Andries et al.* Reference

Scope and Content

The *Andries et al.* reference merely discloses compounds that fall within the scope of the active ingredient of formula I, as defined in claim 1. The reference also discloses that such compounds can be applied in various conventional dosage forms.

Differences between the Reference and Claim 1

[6] MPEP §2143.03, citing *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

The *Andries et al.* reference differs from the present invention, at least because the reference fails:

1. to teach that the active ingredient is present in a polymer matrix as a solid dispersion, and
2. to teach that the particles are obtained by a melt extrusion process.

The *Goertz et al.* Reference

Scope and Content

The *Goertz et al.* reference relates to a process of preparing solid pharmaceutical dosage forms. According to the process, the dosage forms are prepared by mixing a pharmaceutical active compound with a fusible pharmacologically tolerated binder, and optionally other pharmaceutical auxiliaries. The fusible binder, according to *Goertz et al.* is a homo- or copolymer of N-vinylpyrrolidone. The other pharmaceutical auxiliaries are extenders, wetting agents, preservatives, disintegrants, absorbents, colorants and flavorings (see: column 5, lines 38 to 46). According to the *Goertz et al.* process, the mixing occurs at temperatures of from 50 to 180°C, i.e., as a melt or in a softened state. However, the reference makes clear that:

> **The polymeric binder must soften or melt in the total mixture of all components at from 50 to 180° C., preferably from 60° to 130° C., so that the melt can be extruded.** [7]

Finally, the *Goertz et al.* process involves subjecting the mixture to an injection molding an shaping the particles.

Differences between the Reference and Claim 1

[7] Column 2, lines 32 to 37 of Goertz et al. (US 4,801,460).

The *Goertz et al.* reference provides no guidance to prompt a skilled artisan to believe that it would be desirable, or even possible, to produce rate-controlled release particles, which comprise a compound of the formula I to VI, as defined in claim 1, a polymer matrix , and from 5 to 25 % by weight of hydroxypropyl methyl cellulose (HPMC). Compounds of the formula I to VI are not contemplated. HPMC is not contemplated. Of course, since HPMC is not contemplated, a specific amount of HPMC is not contemplated. The Examiner has mischaracterized the scope and content of this reference. A skilled artisan would not have reasonably concluded that it is desirable, or even possible, to produce rate-controlled release particles, as defined in claim 1, using the *Goertz et al.* process merely because the *Goertz et al.* reference provides "no particular limitation as to the active ingredients employed..."[8] Such a statement simultaneously underestimates the level of skill of an person of ordinary skill in the art and overstates the scope and content of the *Goertz et al.* reference. A skilled artisan had no apparent reason to utilize the *Goertz et al.* process to produce rate-controlled release particles, which comprise a compound of the formula I to VI, as defined in claim 1, a polymer matrix, and from 5 to 25 % by weight of hydroxypropyl methyl cellulose (HPMC).

The *Nakamichi et al.* Reference

Scope and Content

The *Nakamichi et al.* reference describes an improved process for producing a solid dispersion of pharmaceutical active ingredients. The improvement described by *Nakamichi et al.* is achieved by employing a particular twin-screw extruder. Indeed, *Nakamichi et al.* make clear that

> The substantive feature of the present invention resides in the processing of the drug, polymer and other components for a solid dispersion by utilizing a twin-screw extruder. [9]

The reference provides a large list of pharmaceutical compounds that might be processed

[8] Page 3, line 19 of the final Office action mailed March 13, 2007.
[9] Column 1, lines 59 to 61 of Nakamichi et al. (US 5,456,923).

utilizing the particular twin-screw that is described. (See: column 3, line 55 to column 5, line 48 of *Nakamichi et al.*). The reference also mentions a large number of possible polymers without giving a preference to a specific polymer. Rather, it is stated that:

> The polymer to be used in the present invention can be virtually any natural or synthetic polymer that can be generally used as a raw material in the manufacture of pharmaceutical products and such that its functions are not adversely affected by the passage through the small die orifice or orifices of the twin-screw extruder. [10]

Differences between the Reference and Claim 1

The *Nakamichi et al.* reference does not address the specific constituents of the rate-controlled release particles. In fact, although the reference provides an enormous list of possible pharmaceutical compounds (see: column 3, line 55 to column 5, line 48), the active ingredients, as defined in claim 1 (formulas I to VI) are conspicuously absent. A skilled artisan had no apparent reason to conclude that the active ingredients, as defined in claim 1, could be used in the process according to *Nakamichi et al.*

Another distinction is that while the reference explains that a large number of polymers could possibly be used, the reference fails to disclose that the particular polymers of claim 1 could be used. Again, the polymer matrix of claim 1 must consist of a homo- or copolymer of N-vinylpyrrolidone, in an amount from 40 to 70 % by weight of the total weight of the particles. A skilled artisan had no apparent reason to conclude that a polymer matrix consisting of a homo- or copolymer of N-vinylpyrrolidone, in an amount from 40 to 70 % by weight of the total weight of the particles, as defined in claim 1, could be used in the process according to *Nakamichi et al.*

Next, the reference provides no guidance to prompt a skilled artisan to believe that it would be desirable, or even possible, to use a polymer (let alone the specifically claimed homo- or copolymer of N-vinylpyrrolidone) in the specifically claimed amount (from 40 to 70 % by weight) in combination with a specific amount (from 5 to 25 % by weight) of hydroxypropyl methyl cellulose (HPMC)

[10] Column 2, lines 32 to 37 of Nakamichi et al. (US 5,456,923).

The *Sasatani et al.* Reference

Scope and Content

The *Sasatani et al.* reference relates to spray-dried granules of pranlukast and one or more saccharides as essential ingredients and further comprising one or more water-soluble polymers and/or surfactants. Possible water soluble polymers include *inter alia* HPMC and polyvinylpyrrolidone. The reference requires that

> The water-soluble polymer is used in an amount of, for example, 1 to 30 parts by weight, preferably 5 to 20 parts by weight, based on 100 parts by weight of pranlukast. [11]

The surfactant can be polyoxyethylene hydrogenated castor oil.[12] A pH adjusting agent may also be added to adjust the pH of the suspension for spray-drying.[13] The reference lists citric acid as a preferred acidic pH adjusting agent.[14]

Differences between the Reference and Claim 1

Pranlukast is not a compound within the formula I to VI, as defined in claim 1. The process of *Sasatani et al.* does not include a melting step. The reference does not disclose particles containing the vinylpyrrolidone containing polymer in amounts from 40 to 70% by weight. The reference does not disclose a combination of a vinylpyrrolidone containing polymer with HPMC.

Thus, the Examiner's statement that the reference "teaches that polyethylene glycol castor oil ester and citric acid are known pharmaceutical excipients and are particularly known to be useful in solid form wherein polyvinylpyrrolidone is carrier"[15] is an gross mischaracterization of the actual scope and content of the *Sasatani et al.*

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[11] Column 5, lines 46 – 48 of Sasatani et al. (US 5,876,760).
[12] See: column 5, lines 49 – 56 of Sasatani et al. (US 5,876,760).
[13] See: column 5, lines 25 – 27 of Sasatani et al. (US 5,876,760).
[14] See: column 5, lines 60 – 62 of Sasatani et al. (US 5,876,760).
[15] Page 4, lines 6 – 8 of the final Office action mailed March 13, 2007.

reference.

At best, *Sasatani et al.* evidences that a specific type of active ingredient (pranlukast) requires specific measures for obtaining suitable solid dosage forms. A skilled artisan would never generalize the specific teaching of *Sasatani et al.* as the Examiner has done. More specifically, a skilled artisan would never conclude that polyethylene glycol castor oil ester and/or citric acid could be used in combination with an active ingredient (for example, a compound according to formula I to VI, as defined in claim 1) that has no similarity, structurally or otherwise, to the specific type of active ingredient of *Sasatani et al.*

The *Takada* et al. Reference

Scope and Content

The *Takada* et al. reference teaches an enteric formulation of a proteinous drug which comprises an intimate mixture of the drug, a nontoxic, non-ionic surfactant, and an enteric material. The enteric material is typically a polymer having free carboxyl groups. According to the reference,

> **The preparation of this invention contains at least 50%, preferably not less than 80% by weight based on the entire composition of an enteric material capable of dissolving in a conventional organic solvent as previously mentioned and also in the duodenal juice.** [16]

According to the *Takada* et al. reference, homo- or copolymers of N-vinylpyrrolidone are not considered to be enteric materials, since polyvinylpyrrolidone is mentioned only as a further conventional pharmaceutical excipient (See: column 4, line 25). Rather, hydroxypropylmethylcellulose succinate and hydroxypropylmethylcellusloe phthalate are mentioned as possible enteric materials (See:column 4, line 16 – 18).

[16] Column 4, lines 4 – 8 of Takada et al. (US 5,350,741).

Differences between the Reference and Claim 1

When properly considered as a whole, the *Takada* et al. reference teaches away from the present invention. The reference requires a high amount, at least 50%, and preferably not less than 80% of an enteric material, such as HPMC. Whereas the rate-controlled release particles of claim 1 must comprise from 5 to 25 % by weight of hydroxypropyl methyl cellulose (HPMC). The reference provides no teaching whatsoever that would prompt a skilled artisan to conclude that reducing the amount of enteric material below the mandatory minimum of 50% would achieve any recognizable result other than rendering an enteric formulation according to *Takada* et al. unsatisfactory for its intended purpose. It is well-settled that "[i]f proposed modification would render the cited art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification."[17]

Moreover, compounds I to VI, as defined in claim 1, are not proteinous drugs. Again, the *Takada* et al. reference teaches an enteric formulation of a proteinous drug which comprises an intimate mixture of the drug, a nontoxic, non-ionic surfactant, and an enteric material.

Additionally, the reference does not teach that the compounds are present as a solid dispersion, and the reference does not teach a process which includes melting of the mixture of polymer and active ingredient.

The *Baert et al.* Reference

Scope and Content

The *Baert et al.* reference relates to a preparation of the pharmaceutical Loviride. The preparation, according to *Baert et al.*, comprises a solid dispersion of Loviride and one or more pharmaceutically acceptable water-soluble polymers.[18]

According to *Baert et al.*,

[17] In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).
[18] Cf. page 2, indicated lines 52 to 55, of EP 0 872 233.

> Tablets that give an immediate release of loviride upon oral ingestion and that have good bioavailability are designed in such a manner that the tablets disintegrate rapidly in the stomach (immediate release) and that the particles which are liberated thereby are kept away from one another so that they do not coalesce and do not produce high local concentrations of loviride with the concommittant danger that the drug precipitates (bioavailability). The desired effect can be obtained by distributing said particles homogeneously throughout a mixture of a disintegrant and a diluent. Suitable disintegrants are those that have a large coefficient of expansion. Examples thereof are hydrophilic, insoluble or porrly water-soluble crosslinked polymers such as crospovidone (crosslinked polyvinylpyrrolidone) and croscarmellose.[19]

Thus, contrary to the Examiner's mischaracterization of the scope and content of the reference, a combination of HPMC and crospovidone (crosslinked polyvinylpyrrolidone) is disclosed. In other words, the *Baert et al.* reference addresses a combination of HPMC and crospovidone rather than a combination of polyvinylpyrrolidone (PVP) and HPMC.

Differences between the Reference and Claim 1

Loviride is structurally distinct from the compounds of the formulae (I) to (VI) referenced in applicants claims. Most notably, Loviride contains only one center of basicity, namely a phenyl bound amino nitrogen, whereas the compounds (I) to (VI) referenced in applicants' claims contain at least one further center of basicity, namely a basic heterocycle which carries an imino nitrogen. Due to these structural distinctions, both the polarity and the basicity of the compounds (I) to (VI) can be expected to be markedly distinct from the corresponding properties of Loviride. A skilled artisan would understand that properties such as the polarity and the basicity have, a strong impact on the dissolution properties of a compound and, correspondingly, on the interaction of the compound with water-soluble polar polymers. A person of ordinary skill in the art would not reasonably expect that means which are suitable to provide for a sustained release dosage form of Loviride will act in an equivalent manner when the active ingredient is replaced by a compound according to applicants' formulae (I) to (VI).

[19] Page 5, line 56 to page 6, line 5 of EP 0872 233.

Moreover, *Baert et al.* address a combination of HPMC and crospovidone rather than a combination of polyvinylpyrrolidone (PVP) and HPMC.[20] Crospovidone is, in contrast to PVP, a hydrophilic, insoluble or poorly water-soluble crosslinked polymer,[21] which acts as a disintegrant and ensures an immediate release of the active ingredient by rapidly disintegrating the preparation in the stomach.[22] The disintegrant properties result because the cross-linked polymer has a large coefficient of expansion which means that crospovidone particles swell upon contact with and aqueous environment and thus destroy the matrix of the solid dispersion. To a skilled artisan, it would be immediately apparent that disintegrants are used only, as pointed out by *Baert et al.*, in *immediate release* preparations.[23]

Nonobviousness of the Claimed Subject Matter

Against the background of the scope and content of the cited art, the differences between the cited art and the claims; and the level of ordinary skill in the pertinent art, at least as set forth above, the nonobviousness of the claimed subject matter should be clear. A skilled artisan had no apparent reason to utilize the *Goertz et al.* process to produce rate-controlled release particles, which comprise a compound of the formula I to VI, as defined in claim 1, a polymer matrix , and from 5 to 25 % by weight of hydroxypropyl methyl cellulose (HPMC). A skilled artisan had no apparent reason to assume that the active ingredients, as defined in claim 1, could be used in the process according to *Nakamichi et al.* A skilled artisan had no apparent reason to assume that a polymer matrix consisting of a homo- or copolymer of N-vinylpyrrolidone, in an amount from 40 to 70 % by weight of the total weight of the particles, as defined in claim 1, could be used in the process according to *Nakamichi et al.* A skilled artisan had no apparent reason to assume that it would be desirable, or even possible, to use a polymer (let alone the specifically claimed homo- or copolymer of N-vinylpyrrolidone) in the specifically claimed amount (from 40 to 70 % by weight) in combination with a specific amount

[20] Cf. page 6, indicated lines 3 to 5, of EP 0 872 233.
[21] Cf. page 6, indicated lines 3 to 5, of EP 0 872 233.
[22] Cf. page 5, indicated line 56, to page 6, indicated line 2, of EP 0 872 233.
[23] Cf. page 5, indicated lines 56 and 57, of EP 0 872 233.

(from 5 to 25 % by weight) of hydroxypropyl methyl cellulose (HPMC) in the process according to *Nakamichi et al.* A skilled artisan had no apparent reason to conclude that polyethylene glycol castor oil ester and/or citric acid could be used in combination with an active ingredient (for example, a compound according to formula I to VI, as defined in claim 1) that has no similarity, structurally or otherwise, to the specific type of active ingredient of *Sasatani et al.* When properly considered as a whole, the *Takada* et al. reference teaches away from the present invention, and the reference provides no teaching whatsoever that would prompt a skilled artisan to conclude that reducing the amount of enteric material below the mandatory minimum of 50% would achieve any recognizable result other than rendering an enteric formulation according to *Takada* et al. unsatisfactory for its intended purpose. A person of ordinary skill in the art had no apparent reason to conclude that *Baert et al.*'s means to provide for a sustained release dosage form of Loviride would act in an equivalent manner when the active ingredient is replaced by a compound according to applicants' formulae (I) to (VI). Since *Baert et al.* address a combination of HPMC and crospovidone rather than a combination of polyvinylpyrrolidone (PVP) and HPMC,[24] and since crospovidone is, in contrast to PVP, a hydrophilic, insoluble or poorly water-soluble crosslinked polymer,[25] which acts as a disintegrant and ensures an immediate release of the active ingredient by rapidly disintegrating the preparation in the stomach,[26] a skilled artisan had no apparent reason to utilize a combination of polyvinylpyrrolidone (PVP) and HPMC. When the scope and content of the cited references is properly ascertained, it is abundantly clear that the references cannot be combined and modified as proposed by the Examiner without violating, contradicting, or ignoring explicit teachings of the references. For at least the reasons discussed above, no apparent reason existed at the time the present invention was made to make the proposed combinations and modifications. Thus, the present rejection is in error and should be withdrawn.

The Examiner has repeatedly urged that the optimization of result effective parameters is deemed to be within the skill in the art. Applicants pointed out that this argument begs the question which of the parameters are effective to achieve a particular

[24] Cf. page 6, indicated lines 3 to 5, of EP 0 872 233.
[25] Cf. page 6, indicated lines 3 to 5, of EP 0 872 233.
[26] Cf. page 5, indicated line 56, to page 6, indicated line 2, of EP 0 872 233.

result. In response, the Examiner has stated that "the rejections state that the optimization of a result effective parameter, e.g. drug releasing profile, or the effective amounts of the drug and other ingredients therein, is considered within the skill of the artisan."[27] This mere statement fails to establish that any parameter in the cited references was considered to be a result effective parameter at the time the claimed invention was made. Before the determination of the optimum or workable ranges of a variable might be characterized as routine experimentation, that particular parameter must first be recognized as a *result-effective variable*, i.e., a variable which achieves a recognized result,[28] The Examiner has not identified a single parameter that achieves a recognized result. Thus, it would be improper for the Examiner to characterize the determination of the optimum or workable ranges of any parameter as a matter of routine experimentation.

In the final Office action of March 13, 2007, the Examiner also rejected claim 26 under 35 U.S.C. §103(a) over *Andries et al.* (US 6,197,779), in view of *Goertz et al.* (US 4,801,460), *Nakamichi et al.* (US 5,456,923), *Sasatani et al.* (US 5,876,760) and *Takada* (US 5,350,741) and in further view of *Baert* (EP 0 872 233), and further in view of *Jones et al.* (US 4,917,900).

The discussion above applies to claim 26 as well, because like claim 1, independent claim 26, as amended, relates to rate-controlled release particles, which comprise:

- a compound of the formula I to VI as an active ingredient,
- a polymer matrix , and
- from 5 to 25 % by weight of hydroxypropyl methyl cellulose (HPMC).

Claim 26, like claim 1, also imposes the following limitations:

- The polymer matrix of claim 1, must consist of a homo- or copolymer of N-vinylpyrrolidone, in an amount from 40 to 70 % by weight of the total weight of the particles.
- The rate-controlled release particles must comprise the active ingredient as a solid dispersion in the polymer matrix.
- The rate-controlled release particles must be obtained by forming a

[27] Page 6 lines 20 – 21 of the final Office action mailed March 13, 2007.
[28] *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

homogeneous mixture of the components in the form of a melt, extruding the mixture, and shaping the extrudate.

Claim 26 imposes the additional limitation that:

- The homo- or copolymer of N-vinylpyrrolidone must have a Fikentscher K value of from 17 to 90.

Regarding *Jones et al.*, the Examiner is again reminded that citing references which merely indicate that the elements and/or features which are recited in a claim are separately known in the art is not a sufficient basis for concluding that the combination of the elements which is defined by the claims would have been obvious to a person of ordinary skill in the art.[29] To render the claimed combination of elements obvious it is also necessary that there be evidence of an apparent reason or motivating force which would impel a person skilled in the art to do what applicants have done. The Examiner has not pointed to any apparent reason for a skilled artisan to any modification whatsoever on the basis of *Jones et al.* The present rejection is in error and should be withdrawn.

In Conclusion:

The present application is in condition for allowance. Again, applicants are thankful for the Examiner's diligent efforts to advance this application to allowance, and request favorable action in this matter. In order to facilitate the resolution of any issues or questions presented by this paper, the Examiner is welcome to contact the undersigned by phone to further the discussion.

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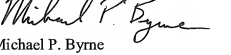

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[29] Cf. *Ex parte Hiyamizu*, 10 USPQ2d 1393 (BPAI 1988).